Synaptogenesis in Layer I of the Human Cerebral Cortex in the First Half of Gestation

The formation of synapses is among the most important steps in neuronal differentiation and the establishment of neuronal circuits. To establish baseline data about the time of onset, density and the course of synaptic formation in different regions of the human cerebral cortex before birth, synaptogenesis in layer I was examined by electron microscopy in fetuses ranging in age from 6 to 24 gestational weeks. Synapses were first observed in the primordial plexiform layer (marginal zone) in both the lateral and medial cerebral walls between the 6th and 7th gestational week, before the formation of the cortical plate. The density of synapses increased rapidly after the formation of the cortical plate, increasing by 37% between 12 and 14 weeks. Synaptogenesis proceeded at the same rate in the lateral and occipital cortex during this period. Further, with one exception, the insular region, synaptic density was comparable in prospective areas of prefrontal, motor, visual, temporal and cingulate cortex in a group of fetuses at midgestation (20 weeks). The results are consistent with a synchronous course of synaptogenesis of the neocortex.

Introduction
The final stage of neuronal differentiation and establishment of complex functions of the neocortex depend heavily on the proper formation of synaptic connections within the cortex, as well as within subcortical structures. A critical number of synapses is essential for the emergence of higher cortical functions, such as learning, memory and cognition (Goldman and Rakic, 1979), and, although some synapses formed before birth are in part transient, they are an essential first step towards the formation of adult cortical circuitry (Knyihar et al., 1979; Purves, 1988). Quantitative data on the onset of synaptogenesis in the human cerebral cortex and the number of synapses at a specific gestational age are useful not only for characterization of normal cortical development, but, in addition, for comparison with the findings obtained from the abnormal human fetal brain. For example, several types of congenital malformations that lead to mental illnesses, ranging from mild cases of ‘minimal brain damage’ to more severe cases of mental retardation, childhood schizophrenia or autism, are related to disturbances of cortical circuitry (Purpura, 1975; Goldman and Rakic, 1979; Volpe, 1987; Rakic, 1988; Bloom, 1993). Therefore, establishing a database for normal human synaptic density will aid in identification of the brain regions that exhibit an abnormal developmental pattern and in pinpointing the gestational stages in which synapse formation diverges from the normal course.

Despite the significance of synapse formation for normal brain function, many aspects of synaptogenesis before birth in humans have been examined in only a fragmentary manner. No quantitative data on synaptogenesis are available for the first half of intrauterine life (Molliver et al. 1973; Larroche, 1981), and only few studies have quantified synaptic density in the second part of gestation (e.g. Kostovic and Rakic, 1980, 1990; Petit et al., 1984; Kostovic et al., 1989). The synaptogenesis in human cortex after birth, which has been more fully documented, proceeds exponentially, reaching a peak at 2 years after birth (Huttenlocher, 1979; Huttenlocher et al., 1982; Huttenlocher and de Courten, 1987). In contrast to the paucity of data in human, quantitative aspects of cortical synaptogenesis have been studied more thoroughly in non-human primates (O’Kusky and Colonnier, 1982; Rakic et al., 1986, Bourgeois et al., 1989, 1994; Zecevic et al., 1989; Zecevic and Rakic, 1991; Zielinski and Hendrickson, 1992; Bourgeois and Rakic, 1993).

The present study was undertaken to generate normative data for the onset and rate of synaptogenesis in the human cerebral cortex during the first half of gestation and to determine whether synaptogenesis proceeds concurrently and in parallel in different cortical regions during this period. In order to determine the rate of synaptogenesis in different cortical areas during the first half of gestation, we estimated the synaptic density in layer I of different regions of the fetal human cortex. This layer was selected because the literature indicates that synaptogenesis starts there first (Molliver et al., 1973; Larroche, 1981). The course of synaptogenesis was analyzed both before the formation of the cortical plate, in the primordial plexiform layer (PPL) and after the formation of the cortical plate, in layer I. In addition, synaptic density in layer I was estimated at midgestation in six regions of the cerebral cortex.

Materials and Methods
Fourteen human fetuses, ranging in age from 12 to 24 gestational weeks (g.w.) were studied using quantitative electron microscopic analysis. In addition seven embryos and fetuses from 6 to 9 g.w. were analyzed for the initial appearance of synapses. The full gestation period in humans is 40 g.w. Human fetuses were obtained with a postmortem delay of 2–5 h from medically indicated abortions that were not expected to involve damage to the fetal central nervous system (Table 1). The tissue was obtained with signed consent, in accordance to institutional guidelines. Fetal age was estimated on the basis of the last menstrual period (weeks after ovulation) and crown–rump length (CRL; Olivier and Pineau, 1962). Five of these fetuses were of approximately the same gestational age of 20 g.w. (Table 1). In this group of five fetuses, two were twins, three were males and two were females.

Blocks (1 × 1 × 1 mm) of cortical tissue were dissected from six different places representing the prospective prefrontal, motor, visual, insular, temporal and cingulate cortex (Fig. 1). It should be noted that for some cases all the mentioned cortical areas were not available, or the tissue was not suitable for quantitative ultrastructural analysis. At the youngest ages examined in this study (6–9 g.w.) the blocks were taken from a cross-section through the cerebral vesicles. This allowed us to study both the medial and lateral telencephalic wall. In a developmental period from 7 to 9 g.w. a pronounced lateromedial gradient of cell maturation was observed in the telencephalic wall. Consequently, at this age the cortical plate was present only in the lateral, but not in the medial wall.

At younger gestational ages included in the quantitative analysis of synaptic density (12–18 g.w.), dissection of cortical areas was performed on the basis of the presumptive location of the areas with respect to gross
structural landmarks (Fig. 1). At this age few landmarks exist on the surface of the brain and the precise location of prospective cytoarchitectonic areas is not distinguishable (Chi et al., 1977; Sidman and Rakic, 1982). However, between 20 and 24 g.w., several distinct landmarks, such as the fossa lateralis, the calcarine and the hippocampal fissures, appeared at the cerebral surface and provided additional guidance for dissection of areas of interest. Nonetheless, because of the primitive maturational state of the cortex in the first half of gestation, some dissected blocks, e.g. for motor and sensory cortical areas, were examined together as the ‘lateral cortex’.

After dissection, tissue blocks were immersed immediately in a fixative of 1% paraformaldehyde and 1.25% glutaraldehyde in 0.1 M phosphate buffer and stored at 4°C overnight. The next day the tissue was rinsed in phosphate buffer, post-fixed in 2% osmium tetroxide for 1 h, stained en block in 2% uranyl acetate, dehydrated in graded alcohols and rinsed in phosphate buffer, post-fixed in 2% osmium tetroxide for 1 h, and embedded in a mixture of Epon and Araldite. Semi-thin sections were cut from all blocks and stained with toluidine blue for evaluation of tissue quality and for proper orientation prior to thin sectioning. Thin sections (~750 μm) were cut across the entire thickness of the cerebral cortex with a diamond knife. The sections were placed on single hole grids covered with Formvar film, stained with uranyl acetate and lead citrate, and examined on a Jeol 100S electron microscope.

The quantitative methodology for estimation of synaptic density has been described in detail previously (Zecевич et al., 1989; Zecевич and Rakic, 1991), and will therefore be described only briefly here. Between 25 and 40 photographs were taken at a magnification of 5000× (final magnification 13 500×) in a random fashion through layer I of each studied cortical area. Layer I was selected as the site for our analysis because synaptogenesis occurs initially in this layer and because layer I is well delineated at all ages examined. A calibration grid (Ted Pella; 2160 lines/mm²) was photographed after analysis of each case to determine the exact magnification. The surface area of each electron micrograph was calculated to be 213–240 μm². The criteria for identification of synapses in electronmicrographs were the presence of apposing, paired membrane thickenings and a synaptic cleft with at least one or more synaptic vesicles.

A major limitation in the study of synaptogenesis in human fetuses is the difficulty in preserving neuronal tissue satisfactorily for the meaningful quantitative analysis on the ultrastructural level. In this study, the overall preservation of human CNS tissue by immersion fixation was superior to the ethanolic phosphotungstic acid (EPTA) method used in previous studies of human synaptogenesis (Huttunen, 1979). For example, we were able to identify pre- and postsynaptic elements, calculate the percentage of neuropil, and measure synaptic length in all cases.

Results

Qualitative Analysis

Both the primordial plexiform layer in young embryos (before the formation of the cortical plate) and, subsequently, layer I,
with their low cellular density and high content of neuropil and extracellular spaces, exhibited a loose arrangement of processes in all cases studied (Figs 2 and 3). In the autopsy material, preservation of layer I was often suboptimal, especially in the narrow stratum situated close to the pia, which contained large extracellular spaces. The extracellular spaces were excluded from neuropil counts, resulting in a low percentage of neuropil in all cases studied. Seven specimens, ranging in age from 6 to 9 g.w., were available for this study, but they were not included in the quantitative analysis due to the very immature state of the synapses and neuropil. Before the formation of the cortical plate at 7–8 g.w., large growth cone profiles filled with vesicles were encountered in the primordium plexiform layer, along with rare synapses. These synapses looked very immature, sometimes containing only vesicles or presynaptic thickenings (Fig. 2). Synapses became more numerous after the cortical plate appeared. Even in later gestational ages, immature looking synapses were observed, but these immature forms were not included in our quantitative analysis due to the very immature state of the synapses and neuropil.

In the upper half of layer I, large Cajal–Retzius (CR) cells were observed in all areas of the cortex at all ages examined. Synapses formed by processes that can be traced to CR cells were encountered, but they were relatively rare. In addition, small neurons and fibers running parallel to the pial surface were present throughout the entire thickness of layer I. In the lower half of this layer, a mesh-like organization was formed by radially directed processes and horizontal fibers running parallel to the pia. Occasionally, the radial processes could be traced to cortical plate neurons, representing their apical dendrites. Many growth cone structures, large in diameter and filled with different size vesicles, were found either on dendritic or axonal processes. Often, one or more synapses could be found on a single growth cone that was directed radially towards the pia (Fig. 3C). Whereas in the first half of gestation immature looking synapses were often encountered, mature synapses were also present, and these had a clearly identified pre- and postsynaptic morphology.

In the majority of these synapses, the presynaptic elements were classified as small diameter axons by their uniform diameter and their content of microtubules. Postsynaptic elements were classified in four groups: dendritic shafts, dendritic growth cones, cell bodies and spines. The majority of synapses in layer I in the first half of gestation were formed between either dendritic growth cones (22–56%) or dendritic shafts (36–70%) and small diameter axons. Synapses on spines were infrequent at this developmental stage (2–7%); 40–48% of all synapses in layer I were symmetric, 30–37% were asymmetric and ∼20% could not be classified due to their immature appearance (Table 2).

Quantitative Analysis of Synaptic Density in Layer I

Quantitative analysis has been done, starting from 12 g.w. onwards, when the number of synapses reached values that made this analysis meaningful. Synaptic density was calculated in three cortical areas: the lateral, the occipital and the interhemispheric region representing motor, visual and cingulate cortex respectively. These three areas were selected from the larger sample because groups of 2–5 fetuses could be formed for different gestational ages, allowing statistical analysis. Synaptic density in the lateral and visual cortex between the youngest group, 12–16 g.w., and the oldest one studied here, 22–24 g.w., increased 38 and 37% respectively, but due to large individual variations and standard errors this did not reach

<table>
<thead>
<tr>
<th>Age (g.w.)</th>
<th>Symmetric</th>
<th>Asymmetric</th>
<th>Unclassified</th>
<th>DS</th>
<th>DSH</th>
<th>GC</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>48</td>
<td>34</td>
<td>18</td>
<td>7</td>
<td>71</td>
<td>22</td>
</tr>
<tr>
<td>20</td>
<td>40.6</td>
<td>37.5</td>
<td>21.9</td>
<td>7.8</td>
<td>36</td>
<td>56.2</td>
</tr>
<tr>
<td>22</td>
<td>48.4</td>
<td>31.45</td>
<td>20.96</td>
<td>7.8</td>
<td>27.5</td>
<td>70.2</td>
</tr>
</tbody>
</table>

*aFetus listed as 20a in Table 1.*
significance. If the uniform rate of synaptogenesis is assumed, synaptic density increased 4% per week in both the lateral and visual cortex. For the cingulate cortex, only the two later age groups were available for analysis, and thus we could not draw any firm conclusions about the rate of synaptogenesis in this short period (Fig. 4). The inter-subject variations were observed in the entire period studied (Fig. 5).

The percentage of neuropil varied between 53 and 33% of the cortical area in all cases studied, but this variation reflected more the differences in preservation of the tissue than any real decline in neuropil density. Synaptic length was 0.23 µm at 12 g.w. and increased significantly to 0.34 µm at 20 g.w. (P < 0.01).

**Synaptic Density in Different Cortical Areas at Midgestation**

At midgestation in a group of five fetuses (n = 5, three males, two females), layer I from four different neocortical regions had similar synaptic densities: prefrontal (32.8 ± 1.3), lateral (32.6 ± 1.8), temporal (33.9 ± 1.3) and visual (32.4 ± 0.99). The synaptic densities of two cortical areas belonging to the mesocortex, i.e. the cingulate (29.5 ± 1.2) and insular (38.8 ± 5.3) cortices, diverged from these four, although the difference was not significant for the cingulate cortex. One-way ANOVA showed that the synaptic density in the insular cortex was higher than either in the lateral (P < 0.05) or the cingulate area (P < 0.001; Dunn’s multiple comparison test). When results were expressed per surface area of neuropil (100 µm²) instead of per unit volume of neuropil the same results were obtained, with the exception that a difference between the prefrontal and insular cortex (P < 0.05) emerged (Table 3). The insular cortex also had the highest variability, as evidenced in Fig. 6. When statistical analysis was done for each fetus in this group separately, three fetuses (marked with an asterisk on Table 3 and Fig. 6) showed differences among various regions of the cortex, whereas the remaining two did not.

In this group of five midgestation fetuses, the percentage of

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**Figure 3.** (A) At 12 g.w. layer I neuropil consists of small, transversely cut axons and longitudinally oriented fibers running parallel to the pia (B). Larger profiles including the growth cone (GC) structures, probably belonging to dendrites (D) of cortical plate cells, were very prominent at 18 g.w. The fact that these growth cone profiles were very often postsynaptic elements suggest that they belong to dendrites and not axons. (C) Example of the growth cone with two synapses, 22 g.w. fetus. Magnification 5000×. (D) Incomplete synapses (arrow and arrowhead) at 12 g.w. Magnification 10 000×. (E) Symmetric synapses on dendritic shaft at 18 g.w. Magnification 8600×. (F) Example of synapses on spine (S) at 22 g.w. Magnification 6000×.
neuropil in the cortex was in the narrow range of 32.7 ± 2.8–36.4 ± 4.8%, and no significant differences were found (P = 0.96). Moreover, synaptic length did not vary within the group of five 20 g.w. fetuses (synaptic length = 0.34 ± 0.02 µm). Thus, the observed difference in synaptic density could not be attributed to variation in either neuropil content or synaptic length.

Two fetuses from this group were twins (260392-I and -II), and they showed a remarkably similar synaptic density in most cortical areas (case 2 and 3 on Fig. 6 and Table 3). In three cases, blocks of the occipital pole were taken from the outer and inner brain surface. Although anatomically separated, both of these areas belong to the future visual cortex. In all examined cases, synaptic counts from the two blocks were very similar, and these synaptic counts were therefore combined for statistical analysis.

**Discussion**

**The Onset and Early Synaptogenesis**

The first synapses were observed in the primordial plexiform layer at both the lateral and medial telencephalic wall between 6 and 7 g.w. Although it is generally considered that the first synapses in the cortical anlage appear above the cortical plate in the developing layer I and below the cortical plate in the transient subplate zone (Molliver et al., 1973; Kostovic and Molliver, 1974), occasional synapses could be observed in the primordial plexiform layer before the formation of the cortical plate (Larroche, 1981; Choi, 1988). Similarly, the early appearance of synapses has been reported in the embryonic telencephalon of other mammals (Balslev et al., 1992, 1996). However, after synapses appear in layer I, there is a rapid—over 35%—increase in synaptic density that occurs between 12 and 24 weeks of gestation. Comparison of synaptic density between six cortical areas at 20 g.w. showed significantly greater synaptic density in the insular cortex than in any other area studied. Although the number of specimens examined was small, these results suggest the possibility that the onset of synaptogenesis may start in the insular cortex in conjunction with the developmental gradients of cellular maturation, which also begins in the insular cortex (Sidman and Rakic, 1973, 1982). However, once the process of synaptogenesis begins to accelerate, the basic rate of synaptic accretion does not differ significantly among cortical areas during the remainder of the fetal period. In this respect, the synchronized rate is analogous to the course of synaptic formation in the monkey cortex in which new synapses are added at the same rate in widespread areas of the cerebral cortex (Rakic et al., 1986, 1994).

Variations in the quality of tissue observed between fetuses of the same age used in this study were directly related to the length of the postmortem delay (2–5 h). However, a certain degree of variability is not unexpected in light of previous studies of cortical development in non-human primates where, in spite of an excellent preservation of tissue, similar differences in synaptic density have been found among animals of the same gestational age (Zecevic and Rakic, 1991; Bourgeois and Rakic, 1993; Rakic et al., 1994). Our present data are also congruent with the variability found in other structural parameters, such as the number of neurons (Vincent et al., 1989) and number of spines on dendrites of pyramidal neurons (Boothe et al., 1979). It should be pointed out that, in the present study, as well as in

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**Table 3**

Mean synaptic density in layer I expressed per 100 µm² of neuropil and per 100 µm² of neuropil (second number) ± SEM in different regions of the cortex at midgestation

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>CRL</th>
<th>Lateral</th>
<th>Visual</th>
<th>Prefrontal</th>
<th>Temporal</th>
<th>Cingulate</th>
<th>Insular</th>
</tr>
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<tbody>
<tr>
<td>(a) 260392</td>
<td>M</td>
<td>160</td>
<td>11.9 ± 1.3</td>
<td>14.4 ± 1.2</td>
<td>11.9 ± 0.9</td>
<td>8.5 ± 0.8</td>
<td>15.8 ± 1.1</td>
<td></td>
</tr>
<tr>
<td>(b) 260392</td>
<td>M</td>
<td>162</td>
<td>8.5 ± 1.0</td>
<td>9.6 ± 0.6</td>
<td>9.2 ± 0.6</td>
<td>9.1 ± 1.2</td>
<td>9.4 ± 0.7</td>
<td>15.8 ± 1.2</td>
</tr>
<tr>
<td>(c) 230287</td>
<td>M</td>
<td>170</td>
<td>24.3 ± 2.9</td>
<td>27.4 ± 1.7</td>
<td>26.9 ± 1.7</td>
<td>30.2 ± 2.4</td>
<td>30.2 ± 4.0</td>
<td>47.8 ± 3.5</td>
</tr>
<tr>
<td>(d) 270591</td>
<td>F</td>
<td>170</td>
<td>8.7 ± 0.8</td>
<td>11.4 ± 0.7</td>
<td>8.4 ± 0.6</td>
<td>12.9 ± 0.8</td>
<td>8.8 ± 0.8</td>
<td>10.6 ± 1.2</td>
</tr>
<tr>
<td>(e) 260691</td>
<td>F</td>
<td>175</td>
<td>14.8 ± 1.5</td>
<td>17.7 ± 0.9</td>
<td>10.1 ± 0.7</td>
<td>12.3 ± 0.8</td>
<td>12.5 ± 0.9</td>
<td>10.9 ± 0.9</td>
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</tbody>
</table>

Mean ± SEM 167.4 ± 2.8 11.2 ± 0.6 11.3 ± 0.3 11.1 ± 0.4 11.6 ± 0.4 9.9 ± 0.4 13.2 ± 1.4

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*a*Midgestation is 20 g.w. (Full gestation is 40 g.w.).

*b*(a)–(e) correspond to fetuses listed in Table 1.

*c*Three fetuses that showed difference in synaptic density among cortical areas.

n = number of fetuses studied.
previous studies in humans, subjects of mixed gender have been examined, and therefore we cannot exclude the possibility that some of the variability may be due to gender differences. The inter-subject variations observed in developmental studies underscore the necessity of examining additional specimens of the same fetal age and the same gender, a condition which is difficult to fulfil in studies dealing with human fetal tissue.

Although large extracellular spaces were observed in layer I, due to the imperfect fixation of the autopsy material, it is unlikely that this could account entirely for the recorded variability in synaptic density. In the present study, synaptic density was expressed per unit volume of neuropil rather than per area of the cortex, thereby diminishing the effect of possible bias of ‘dilution’ of the estimated synaptic density due to the uneven preservation of neuropil and the magnitude of the extracellular space, or due to uneven growth of brain compartments in the period studied.

Synaptic Density in Different Cortical Areas
At 12 g.w., the youngest fetal age where synapses were quantified, cortical neurons are still actively migrating in the cortical plate, whereas at 24 g.w., the oldest fetal age examined, cortical neurons have already reached their final position in the cortical plate (Marin-Padilla, 1970; Sidman and Rakic, 1973; Rakic, 1977; Mrzljak et al., 1988). These critical stages of cortical development in human correspond to the precortical and early phases of corticogenesis that have been described in the embryonic monkey cerebrum and precede the onset of the rapid, exponential phase of synaptogenesis (Bourgeois et al., 1994). Therefore, the relatively low synaptic density observed throughout the first half of intrauterine life studied here can be expected for this early phase of development.

Regional differences in synaptic density across various cortical areas were studied by analyzing two aspects of synaptogenesis: the rate of synaptogenesis and the synaptic density in fixed time points of development. The rate of synaptogenesis, defined as the change of synaptic density over time, was analyzed in two cortical areas (lateral and occipital) which have different cellular, biochemical and functional proprieties, as well as different afferent and efferent connections (Peters and Jones, 1984). We found that the basic rate of synaptogenesis was not different in these two cortical regions, which is in accord with results reported for monkey cortex before and after birth (Rakic et al., 1986). In contrast, other...
investigators have argued that the rate of cortical synaptogenesis after birth may proceed sequentially from the motor to visual and, finally, prefrontal areas (Huttenlocher, 1979; Huttenlocher et al., 1982; Huttenlocher and de Courten, 1987). In the present study, the synaptic density at midgestation in five out of six cortical areas fell in the narrow range of ∼30–34 synapses per volume unit of neuropil. Although the insular cortex had a higher synaptic density than at least two other cortical areas studied, the small number of specimens collected from the insular cortex does not permit a meaningful statistical analysis or comparison between age groups. However, it is possible that the greater difference in synaptic density observed in the insular cortex may be related to the earlier onset of synaptogenesis in this region, an interpretation consistent with previously described developmental gradients of cellular maturation (Sidman and Rakic, 1982; Smart and McSherry, 1982, McSherry and Smart, 1986). Other examples in which synaptogenesis follows a sequence of developmental events are the inside-out gradient of synaptic formation observed in the cortical plate (Zecevic et al., 1989; Voigt et al., 1993; Bourgeois et al., 1994) and the latero-medial and rostro-caudal developmental gradients of cellular maturation described in ferret cortex (Voigt et al., 1993). It is possible that the onset of synaptogenesis requires a certain level of neuronal differentiation in order to be initiated, but once it starts synapse formation proceeds synchronously over the entire cortical mantle, as was described in monkey (Rakic et al., 1986). This may be a biological necessity for the formation of complex synaptic architecture which depends on competition between various inputs (Rakic, 1981; Shatz, 1996). To compete for available neural targets, synapses need to be present simultaneously at the terminal fields.

Comparison of Synaptic Densities in Fetal Human and Monkey Neocortex

The present study deals with the period before the onset of the rapid increase in cortical synapses, and thus cannot be compared directly to previous studies in either humans or monkey. However, our results extend the analysis of synaptogenesis to the early prenatal period and indicate that during the first half of gestation the rate of synaptogenesis is not significantly different among the cortical regions studied.

When synaptic density in layer I is compared in monkey and human fetuses at midgestation, the synaptic density recorded in humans is almost three times higher. In the monkey, where the gestational period lasts 165 days, synaptic density was reported in the lateral cortex to be 3.26 per 100 µm² of neuropil at midgestation (Zecevic et al., 1989), whereas in humans at midgestation (20 g.w.) it is 11.0 ± 1.5/100 µm² of neuropil. Due to the longer gestational period in humans, it is not easy to compare equivalent time points in the two species. For example, in humans, the period starting from the onset of synaptogenesis (7 g.w.) and extending to midgestation (20 g.w.) lasts ∼3 months, whereas in monkeys synaptogenesis begins around 53 embryonic days, which is only 1 month prior to midgestation. However, the rate of synaptogenesis in the first half of the intrauterine period in human, calculated here to be ∼4% per week, is remarkably similar to 5% reported for monkey motor cortex (Zecevic et al., 1989).

Notes

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